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EXAMINER	
WOOLWINE, SAMUEL C	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,628	HINNAH ET AL.	
	Examiner	Art Unit	
	SAMUEL C. WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *42,44-46,58,65,72,73 and 75* is/are allowed.

6)☒ Claim(s) *41,43,47-50,52-57,59-64,66-71,74 and 76-81* is/are rejected.

7)☒ Claim(s) *51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 June 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Applicant's response filed 07/27/2009 is acknowledged.

The objection to the drawings made in the Office action mailed 10/01/2008 is maintained for the reasons discussed below.

As all previous claims have been cancelled and new claims are presented, all previous rejections are withdrawn over the cancelled claims. Therefore, all rejections in this Office action are new rejections necessitated by amendment.

Drawings

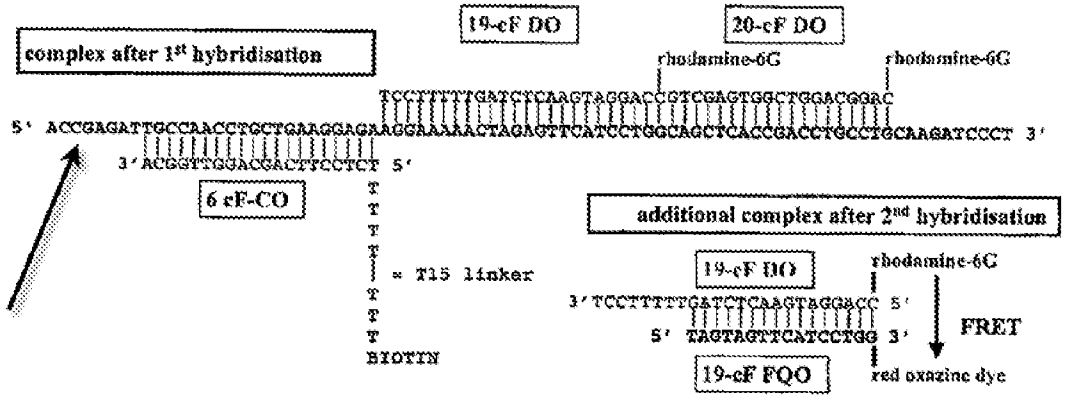
The drawings are objected to because figure 4 contains nucleic acid sequences not identified with sequence identifiers. 37 CFR 1.821(d) states:

> "Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application."

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering

of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

With regard to Applicant's amendments to the specification to provide SEQ ID NOs in the description of figure 4, these amendments are acceptable. However, there are two problems. First, the sequence indicated by the arrow below still has no SEQ ID NO either in the figure or in the description of the figure:



Second, the sequence indicated as 19-cF FQO in the figure was ascribed SEQ ID NO:44 in the amendment to the specification made on 04/01/2009. However, according to the sequence listing, SEQ ID NO:44 has the sequence: tagagttcatcctgg, whereas the sequence in the figure is: tagTagttcatcctgg (where the capitalized T is not found in SEQ ID NO:44). This would appear to require a correction to the sequence listing, as well as the addition of the other sequence (indicated by the arrow above) to

the sequence listing if it is not already present therein. In any event, the drawing is still not in compliance with 37 CFR 1.821(d). The examiner has no objection to an amendment to the specification such as was made on 04/01/2009 in lieu of a correction to the figure itself. However, since the sequence indicated by the arrow above does not have a convenient label in the figure as do the other sequences, it is not clear how this amendment should be made.

Claim Interpretation

Claim 42 recites "a method for detecting an analyte in a sample comprising, in a homogeneous format, the following steps…". In the Office action mailed 10/01/2008, the examiner stated that, as there was no explicit definition of "homogeneous format" in the specification, the term did not distinguish over the prior art (OA 10/01/2008 at page 11). The examiner has reconsidered this position. As stated in MPEP 2111.02: "If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999)." Here, the claim preamble clearly recites the method is performed in a "homogeneous format". Absent an explicit definition in the specification, the term "homogeneous format" must be given its plain meaning as would have been understood by one of ordinary skill in the art (MPEP 2111.01 (I) and (III)). For example, Tyagi et al (WO 95/13399, page 2) state "By 'homogeneous' we mean assays that are performed without separating unhybridized probes from probe-target hybrids." Mabile et

al (US 2002/0177235) state (paragraph [0040]): " 'Homogeneous method' is understood as meaning an assay method in which the measurement does not require the prior separation of the constituents of the assay." Deininger et al (US 6,544,730) state (column 4, lines 13-15): "By 'homogeneous' is meant that the process does not require a separation of the detected target nucleic acid from nontargeted materials." Therefore, a washing or separation step performed prior to the detection step would not be "homogeneous" according to the use of the term by the ordinary practitioners in the art.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 52, 55, 56, 59, 61, 63, 67, 68, 70, 78 and 79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 52 recites "wherein the second hybridization conditions do not…". There is insufficient antecedent basis for this limitation in the claim. Claim 52 depends from claim 50, which does not recite any "second hybridization conditions". For purposes of examination over the prior art, the examiner will assume claim 52 depends from claim 51.

Claim 55 recites "wherein the capture oligonucleotides comprise a first affinity unit capable of binding to a second affinity unit attached to the solid support". This does not comport with the requirement of claim 53, from which claim 55 depends, wherein the capture oligonucleotides are *covalently bound* to the solid support. For purposes of

examination over the prior art, the examiner will assume claim 55 depends from claim 54.

Claim 56 recites "wherein the first affinity unit is biotin and the second affinity unit is streptavidin or avidin". There is insufficient antecedent basis for this limitation in the claim. Claim 56 depends from claim 54, which recites an "affinity interaction", but does not recite any "first affinity unit" or "second affinity unit". For purposes of examination over the prior art, the examiner will assume claim 56 depends from claim 55.

Claim 59 recites "wherein the difference in the excitation wavelength and/or emission wavelength between first and second reporter is at least 10 nm". There is insufficient antecedent basis for this limitation in the claim. Claim 59 depends from claim 57, which depends from claim 43, which depends from claim 41. None of these claims recite any "second reporter". For purposes of examination over the prior art, the examiner will assume claim 59 depends from claim 58.

Claim 61 recites "linking the sequence of the capture oligonucleotide complementary to the analyte with the affinity unit or the solid support." There is insufficient antecedent basis for this limitation in the claim. Claim 61 depends from claim 43, which depends from claim 41. None of these claims recites any "affinity unit". For purposes of examination over the prior art, the examiner will assume claim 61 depends from claim 55. Because claim 63 and 78 depend from claim 61, they are rejected for the same reasons.

Claim 63 recites "wherein the different sets of detection oligonucleotides are labeled with different reporters". There is insufficient antecedent basis for this limitation

in the claim. Claim 63 depends from claim 61, which does not recite any "different sets" of detection oligonucleotides. For purposes of examination over the prior art, the examiner will assume claim 63 depends from claim 62.

Claim 67 recites "wherein the first reporter is a donor of a Forster resonance energy transfer (FRET) donor-acceptor-pair and the quenching unit is an acceptor…". There is insufficient antecedent basis for this limitation in the claim. Claim 67 depends from claim 65, which depends from claim 44, which depends from claim 42. None of these claims recite any "quenching unit". For purposes of examination over the prior art, the examiner will assume claim 67 depends from claim 66.

Claim 68 recites "wherein the quenching unit is…". There is insufficient antecedent basis for this limitation in the claim. Claim 68 depends from claim 65, which depends from claim 44, which depends from claim 42. None of these claims recite any "quenching unit". For purposes of examination over the prior art, the examiner will assume claim 68 depends from claim 66 or 67. Because claim 70 depends from claim 68, it is rejected for the same reason.

Claim 70 recites "wherein the quantification is performed by…". There is insufficient antecedent basis for this limitation in the claim. Claim 70 depends from claim 68, which depends from claim 65, which depends from claim 44, which depends from claim 42. None of these claims recites any "quantification". For purposes of examination over the prior art, the examiner will assume claim 70 depends from claim 69.

Claim 78 recites "wherein the capture oligonucleotides of different sets are…". There is insufficient antecedent basis for this limitation in the claim. Claim 78 depends from claim 61, which depends from claim 43, which depends from claim 41. None of these claims recites any "different sets" of capture oligonucleotides. For purposes of examination over the prior art, the examiner will assume claim 78 depends from claim 62.

Claim 79 recites "wherein the solid supports differ in the affinity units attached thereto...". There is insufficient antecedent basis for this limitation in the claim. Claim 79 depends from claim 77, which depends from claim 43, which depends from claim 41. None of these claims recites any "affinity units". Furthermore, none of the claims recites "solid supports" (i.e. a plurality). Claim 41 only recites "a solid support". For purposes of examination over the prior art, the examiner will assume claim 79 depends from claim 55 (although there is still an issue with regard to "solid supports" vs. "a solid support").

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 41, 43, 48, 50, 54-57, 60, 61, 66-68, 74, 76, 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urdea et al (Nucleic Acids Research 16(11):4937-4956, 1988) in view of Li et al (Nucleic Acids Research, Vol. 30, No. 2 e5, January 15, 2002, pp 1-9, prior art of record) and as evidenced by Yamamoto (US 2008/0213762, prior art of record).

With regard to claims 41, 43, 74 and 76, Urdea taught detection probes labeled with a first reporter, which detection probes were capable of binding an analyte (i.e. a nucleic acid "target"; see figure 2). Urdea taught a solid support (bead support; see figure 2). Urdea taught capture probes bound to the bead support, which capture probes were capable of binding the analyte (see figure 2). Urdea taught contacting the sample with the detection probes, the solid support and the capture probes to form a hybrid between the detection probes and the analyte, and detecting the detection probes (see figure 2). Urdea taught the reporter could be a fluorescent dye (page 4942, 2nd full paragraph, for example).

With regard to claim 50, Urdea taught first hybridization conditions allowing a stable hybrid between detection oligonucleotides and analyte (section entitled "Sandwich hybridization assay procedure" beginning on page 4944).

With regard to claims 54-56, Urdea taught an affinity interaction between avidin on the bead support and biotin on the capture probe (see figure 2).

With regard to claim 57, Urdea taught a bead (see figure 2).

With regard to claim 60, Urdea taught an alkylamine linker for linking the detection oligonucleotide to the reporter (page 4938, 2nd and 3rd full paragraphs, figure 1).

With regard to claim 61, Urdea taught the biotin was attached to the capture oligonucleotide as a "long chain" N-hydroxysuccinimidyl biotin (page 4941: "Biotin derivatization). The long chain qualifies as a linker.

With regard to claim 77, Urdea stated that "all oligonucleotides were synthesized" (page 4940, last column). Hence, the sample was an in vitro prepared sample.

Urdea did not teach detecting the detection probes in the presence of quenching probes binding to surplus detection probes not bound to the analyte thereby quenching at least partially an emission of the first reporter of the surplus detection probes (as recited in claim 41). Urdea did not teach that the hybrid between detection oligonucleotide and analyte has a higher melting temperature than the hybrid between detection oligonucleotide and quenching oligonucleotide (as recited in claim 48). Urdea did not teach quenching oligonucleotides with quenching units (as recited in claim 66). Urdea did not teach a FRET pair (as recited in claim 67, which the examiner assumes should depend from claim 66; see rejection under § 112, 2nd paragraph above). Urdea did not teach a "dark quencher" (as recited in claim 68, which the examiner assumes should depend from claim 66; see rejection under § 112, 2nd paragraph above).

With regard to claims 41 and 66, Li taught double-stranded probe complexes comprised of a longer oligonucleotide (detection oligonucleotide) complementary to a target (analyte) and labeled with a fluorophore (first reporter), and a shorter oligonucleotide (quenching oligonucleotide) labeled with a quencher (see figure 2). The probe complex is designed such that in the absence of a target, the two strands of the complex remain associated with one another, quenching the fluorescence of the fluorophore (see figure 2 and page 3, "Design and preparation of double-stranded probes"). However, in the presence of a target, the longer duplex formed by the detection oligonucleotide and target is thermodynamically favored over the shorter duplex formed by the detection oligonucleotide and quenching oligonucleotide (see figure 2 and page 2, "Reaction kinetics with double-stranded probes"). Hence, Li's probes are designed to be used such that detection occurs in the presence of quenching probes binding to surplus detection probes not being bound to the analyte and thereby quenching at least partially an emission of the first reporter of said surplus detection probes.

With regard to claim 48, since the hybrid formed by the labeled strand (i.e. the detection oligonucleotide) of Li's probe complex with the target is longer (i.e. comprises more base-paired nucleotides) than is the hybrid formed by the labeled and quencher strands of the probe complex, the former inherently has a higher melting temperature than the latter.

With regard to claim 67, Li's probe complex comprised a FRET pair; e.g. see figure 5 caption: FAM/dabcyl, HEX/dabcyl, TAMRA/dabcyl, and Texas Red/dabcyl are all FRET pairs.

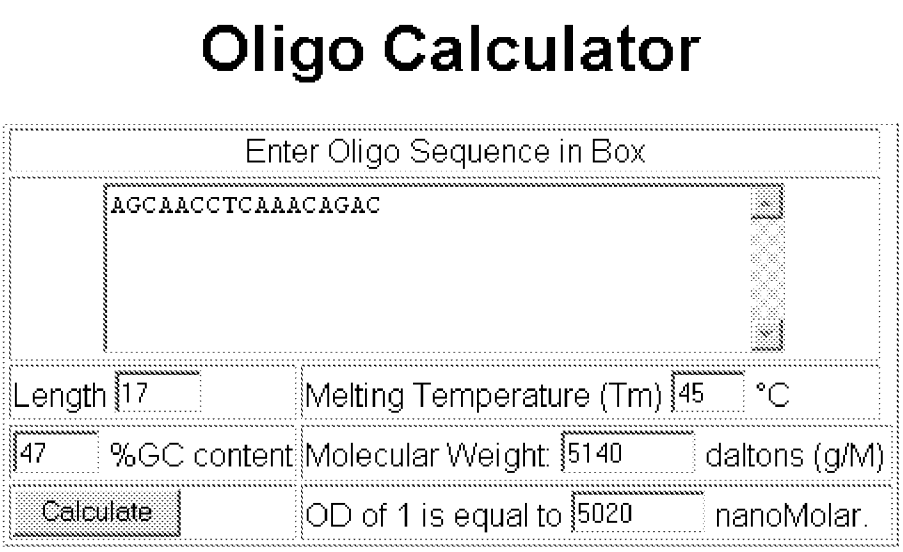
With regard to claim 68, Li taught dabcyl (see figure 5 caption), which as evidenced by Yamamoto (paragraphs [0050], [0097], [0100]), is a dark quencher.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Urdea by substituting the detection probes used by Urdea with the detection probe/quencher complexes taught by Li, because Li taught these complexes enhanced specificity (page 1, last paragraph), and because Li taught that these complexes provided much higher sensitivity (page 6, next-to-last paragraph). Li stated (abstract): "This class of probes should find applications in a variety of areas wherever high specificity of nucleic acid hybridization is relevant."

Claims 47, 49, 53, 62-64, 69-71, 78, 80 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urdea et al (Nucleic Acids Research 16(11):4937-4956, 1988) in view of Li et al (Nucleic Acids Research, Vol. 30, No. 2 e5, January 15, 2002, pp 1-9, prior art of record) as applied to claims 41, 43, 48, 50, 54-57, 60, 61, 66-68, 74, 76, 77 above, and further in view of Yang et al (US 2002/0034753).

The teachings of Urdea and Li have been discussed. With regard to claim 49, Li taught that the reaction rate was maximal when the labeled strand of the probe exceeded the quencher strand by 7 nt (see page 2, "Reaction kinetics with double-

stranded probes"). The probe having a 7 nt difference between the longer and shorter strands is shown in figure 1A, middle panel of the bottom row. In the hybridized probe complex, base pairing occurs between the sequence AGCAACCTCAAACAGAC of the longer strand and the complementary sequence of the shorter strand. This hybrid has a T_m of 45°C as calculated by the algorithm at http://www.pitt.edu/~rsup/OligoCalc.html:



In the hybrid formed between the longer strand of the probe complex and the target, base pairing would occur between the whole length of the longer probe strand and complementary sequence in the target (i.e. over the sequence AGCAACCTCAAACAGACACCATGG). This hybrid would have a T_m of 57°C, which is at least 10°C higher.

Urdea did not teach that the solid support (i.e. the bead) was also labeled with a fluorescent dye (as recited in claim 47).

Urdea did not teach covalent attachment of the capture oligonucleotides to the solid support (as recited in claim 53).

Urdea did not teach that at least two different analytes were detected by providing at least two different sets of detection oligonucleotides and at least two different sets of capture oligonucleotides (as recited in claim 62), that different sets of detection oligonucleotides were labeled with different reporters (as recited in claim 63), that all detection oligonucleotides of a particular set were labeled with the same reporter (as recited in claim 64), or that the different sets of capture oligonucleotides were attached to different solid supports (as recited in claim 78).

Urdea did not actually teach "quantifying" the analyte (as recited in claims 69-71). Urdea merely determined the detection limit of the assay using known quantities of target, probes, etc.

Urdea did not teach adding a substance to a cellular sample and analyzing whether the substance induced, inhibited or modulated the generation of the analyte (which can be considered a "side effect" of the substance) (as recited in claims 80 and 81).

Yang taught a method of analyzing a nucleic acid sample comprising providing a solid support having capture probes attached thereto, hybridizing with a first segment of a target sequence, and hybridizing a labeled probe to a second segment of the target sequence (paragraphs [0004], [0006], [0013]). With regard to claim 47, Yang taught the beads could be labeled with fluorescent dyes, and that different classes of beads could be distinguished based on their being labeled with different dyes (paragraph [0007]).

With regard to claim 53, Yang taught the oligonucleotides could be covalently attached to the beads (e.g. paragraph [0066]).

With regard to claims 62-64, Yang taught that each different class of microbeads corresponded to a different target nucleic acid (paragraph [0007]). This implicitly taught a different capture oligonucleotide and detection oligonucleotide, since different target nucleic acids would necessarily require different capture probes and detection probes. See also paragraph [0037]. Furthermore, it is noted that Li taught different "sets" of detection oligonucleotides, each set having a different reporter, wherein each detection oligonucleotide belonging to a particular set had the same (identical) reporter (which therefore inherently had the same excitation and emission wavelengths). See figure 5, where Li describes four different sets of detection oligonucleotides: one having the reporter FAM, one having the reporter HEX, one having the reporter TAMRA, and one having the reporter Texas Red.

With regard to claim 78 (which the examiner presumes should depend from claim 62 rather than claim 61; see rejection under § 112, 2nd paragraph above), see paragraph [0037].

With regard to claims 69-71, Yang taught "quantifying the label associated with the target nucleic acid" (paragraph [0007]).

With regard to claims 80 and 81, Yang taught using the method to screen the effect of a substance on the expression of a target nucleic acid (i.e. the generation of the analyte; see paragraphs [0014], [0016], [0017]).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to modify the method suggested by the combined teachings of Urdea and Li by incorporating a label into the beads, in order to take

advantage of the multiplexing ability taught by Yang (e.g. paragraph [0037]). It would have been obvious to covalently attach the capture probes to the beads as taught by Yang since was clearly an art-recognized alternative to the biotin/avidin attachment used by Urdea (Yang taught biotin/streptavidin as well; paragraph [0058]). Furthermore, covalent attachment would have offered an advantage in that a covalent bond would be able to withstand conditions of elevated temperature or other conditions which would denature the avidin or streptavidin, resulting in dissociation from the biotin. It would have been obvious to use different sets of capture probes on different beads, along with different detection oligonucleotides, in order to multiplex, as discussed by Yang (e.g. paragraph [0037]). It would have been obvious to quantify, rather than merely detect, the analytes, as the former clearly would provide more information. Finally, it would have been obvious to use the method to screen the effect of a substance on a cellular sample, since Yang had already contemplated this use for a bead-based sandwich hybridization assay.

Claim 79 is rejected under 35 U.S.C. 103(a) as being unpatentable over Urdea et al (Nucleic Acids Research 16(11):4937-4956, 1988) in view of Li et al (Nucleic Acids Research, Vol. 30, No. 2 e5, January 15, 2002, pp 1-9, prior art of record) and Yang et al (US 2002/0034753) as applied to claims 47, 49, 53, 62-64, 69-71, 78, 80 and 81 above, and further in view of Kachab et al (US 2003/0082571, filed April 8, 2002, priority date April 10, 2001, prior art of record).

The teachings of Urdea, Li and Yang have been discussed. Given the lack of antecedent basis for the limitations of claim 79 (see rejection under 35 U.S.C. 112, 2nd paragraph above), the examiner can only presume that claim 79 requires multiple solid supports, each type having a different affinity unit attached thereto. This was not taught by Urdea, Li or Yang.

Kachab taught it was known in the art to use affinity interactions such as biotin/avidin (paragraph [0002]) to attach a ligand capable of binding an analyte to a solid support (paragraph [0004]: "these capture systems have been applied in assay platforms whereby one component of the capture system is usually conjugated to a ligand capable of binding specifically to the analyte (anti-analyte) with another component of the capture system being immobilised on a solid support…the binding pair involving immobilization to the solid support has a binding specificity which is irrelevant to or independent of the binding specificity of the analyte/anti-analyte interaction of interest"). Kachab taught that other such irrelevant binding pairs include "immunoglobulins and protein A or G" (paragraph [0006]). Kachab taught at paragraph [0007] (emphasis provided, citations omitted):

> "Many different single stage capture systems are available for use as irrelevant binding pairs either for the capture of analytes or analyte/anti-analyte complex species or simply for the immobilisation of anti-analytes or other capture species on a solid support or in a sandwich format of some kind to facilitate detection of the analyte or analyte/anti-analyte complex. It will be appreciated that these capture systems are limited in their applicability as irrelevant binding pairs to systems where multiple analytes, or multi-analyte/anti-analyte complexes or multiple capture species need to be either captured or immobilised on a solid support discretely at specific identifiable capture zones for each of the analytes or analyte/anti-analyte complexes or capture species from a single mixture in solution. In this respect, more than one capture system needs to be used concurrently to achieve the discrete capture needed."

Kachab's solution to this problem was to construct "irrelevant binding pairs" composed of complementary oligonucleotides (paragraph [0008], emphasis provided):

> "Complementary nucleic acid binding pairs represent an additional capture system which may be employed as irrelevant binding pairs…Since only nucleic acids having complementary sequences will hybridise with highest specificity and affinity, and since millions of different binding pairs of nucleic acids having sequences and different lengths can be generated…this capture system lends itself well for use in the applications described above…Applications also include multiple analyte or multiple analyte/anti-analyte capture and detection and multiple analyte or capture species (for example antibody) immobilisation on various supports."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use numerous different binding pairs of complementary nucleic acid sequences as affinity interactions to immobilize the capture probes to the solid supports (i.e. "capture particles") when practicing the method by the combined teachings of Urdea, Li and Yang, since Yang suggested analyzing different analytes in multiplex fashion by attaching different capture probes to different solid supports (e.g. paragraph [0037]). Immobilizing multiple different capture reagents to their respective capture particles in a single reaction, rather than performing a separate immobilization reaction for each different capture reagent/capture particle, would clearly have been more efficient. This would have been a situation where "more than one capture system needs to be used concurrently to achieve the discrete capture needed" as suggested by Kachab.

Claims 41, 43 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edman et al (US 6,589,742) in view of Li et al (Nucleic Acids Research, Vol. 30, No. 2 e5, January 15, 2002, pp 1-9, prior art of record).

With regard to claims 41 and 43, Edman taught an assay for detecting a target nucleic acid in a sample comprising providing capture probes (immobilized on an array) and detection probes (see e.g. figure 2C-D, column 19, lines 8-15, column 23, line 34 through column 24, line 4).

With regard to claim 69, Edman taught quantifying the analyte (column 32, line 48 through column 33, line 12: "The fluorescence present at each site was then quantified.").

Edman did not teach detecting the detection probes in the presence of quenching probes binding to surplus detection probes not bound to the analyte thereby quenching at least partially an emission of the first reporter of the surplus detection probes (as recited in claim 41).

Li taught double-stranded probe complexes comprised of a longer oligonucleotide (detection oligonucleotide) complementary to a target (analyte) and labeled with a fluorophore (first reporter), and a shorter oligonucleotide (quenching oligonucleotide) labeled with a quencher (see figure 2). The probe complex is designed such that in the absence of a target, the two strands of the complex remain associated with one another, quenching the fluorescence of the fluorophore (see figure 2 and page 3, "Design and preparation of double-stranded probes"). However, in the presence of a target, the longer duplex formed by the detection oligonucleotide and target is thermodynamically favored over the shorter duplex formed by the detection oligonucleotide and quenching oligonucleotide (see figure 2 and page 2, "Reaction kinetics with double-stranded probes"). Hence, Li's probes are designed to be used

such that detection occurs in the presence of quenching probes binding to surplus detection probes not being bound to the analyte and thereby quenching at least partially an emission of the first reporter of said surplus detection probes.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Edman by substituting the detection probes used by Edman with the detection probe/quencher complexes taught by Li, because Li taught these complexes enhanced specificity (page 1, last paragraph), and because Li taught that these complexes provided much higher sensitivity (page 6, next-to-last paragraph). Li stated (abstract): "This class of probes should find applications in a variety of areas wherever high specificity of nucleic acid hybridization is relevant."

Claim 72 is rejected under 35 U.S.C. 103(a) as being unpatentable over Edman et al (US 6,589,742) in view of Li et al (Nucleic Acids Research, Vol. 30, No. 2 e5, January 15, 2002, pp 1-9, prior art of record) as applied to claims 41, 43 and 69 above, and further in view of Curry et al (US 2003/0219151).

The teachings of Edman and Li have been discussed. These references did not teach determining an intensity of a background emission in the vicinity of the solid support and considering such intensity when determining the amount of detection oligonucleotides (as recited in claim 72).

Curry taught optical scanning to detect fluorescent emission on nucleic acid hybridization arrays (e.g. figure 6, paragraph [0010]). In addition, Curry taught (paragraphs [0017]-[0018]):

"The background signal generated during scanning regions of the surface of a molecular array outside of the areas corresponding to features arises from many different sources, including contamination of the molecular -array surface by fluorescent or radioactively labeled or naturally radioactive compounds, fluorescence or radiation emission from the molecular -array substrate, dark signal generated by the photo detectors in the molecular -array scanner, and many other sources. When this background signal is measured on the portion of the array that is outside of the areas corresponding to a feature, it is often referred to as the "local" background signal.

An important part of molecular -array data processing is a determination of the background signal that needs to be subtracted from a feature."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to determine an intensity of a background emission in the vicinity of the solid support where the capture probes were immobilized (i.e. the "feature") and to consider such intensity when determining the amount of detection oligonucleotides, because Curry taught this was "an important part of molecular-array data processing".

Allowable Subject Matter

Claims 42, 44-46, 58, 65, 73 and 75 are allowed. Claim 59 would be allowable if amended to depend from claim 58 (which would also obviate the rejection of claim 58

under §112, 2nd paragraph). The closest prior art is Kelso (US 2003/0129296), who taught a sandwich assay for detecting an analyte (paragraphs [0108]-[0109]), and who also taught using an image of the capture particles based on a reference dye in the particles as a mask for processing a corresponding image based on the target fluorescence (paragraphs [0189]-[0190]). However, Kelso does not teach or suggest a "homogeneous format", since he included washing steps (paragraphs [0183]-0184]). While performing assays in a homogeneous format were known to provide advantages (e.g. saving time by elimination of washing or separation steps), the fact that Kelso did include washing steps, and offered no suggestion to do otherwise, would not have provided a reasonable expectation of success in carrying out his method in the absence of washing steps.

Claim 51 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Li taught the probe and quencher strands used together as a complex, allowing the thermodynamically favored target:probe hybrid to compete against the quencher:probe hybrid in a single hybridization condition. There is no teaching or suggestion in the prior art to add the probe under first hybridization condition, then add the quencher under a second hybridization condition. Claim 52 appears as though it should depend from claim 51; this would obviate the rejection of claim 52 under §112, 2nd paragraph.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL C. WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637

/Young J Kim/
Primary Examiner, Art Unit 1637